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Tissue-Specific DNA Methylation Signatures of Alcohol Use Disorder in Human Brain

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Alcohol use disorder (AUD) is a common psychiatric disorder in the United States and has a growing number of associated genomic loci. AUD is 50-60% heritable, and long-term alcohol use has been associated with epigenomic-driven synaptic plasticity changes that promote reward in addiction. Previously, we have shown differential methylation signals between AUD and non-AUD brains in the nucleus accumbens (NAc) and dorsolateral prefrontal cortex (DLPFC). High heterogeneity of methylation signal was observed for many EWAS hits, suggesting the potential for both tissue-specific and shared associations with AUD. To address this question, we used a two-way repeated measures ANOVA on data from 115 decedents (cases = 58, controls = 57) of European ancestry to simultaneously model within subject differences in methylation across brain tissues and between subject differences in AUD status. Illumina EPIC methylation array data for NAc and DLPFC were separately pre-processed with 768,826 CpGs common to both regions used for modeling. Using this modeling approach, and a nominal $p < 0.001$, we identified 276 CpGs associated with AUD with effects shared across brain regions and 409 CpGs significant for interaction between brain region and AUD status, implicating tissue-specific associations. Tissue-specific associated CpGs are located near synaptic genes including *PTPRF, ERBB2,* and *NRXN3* implicating these methylation signals of AUD status on the neurobiological state within and across addiction-relevant brain regions.